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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	10.05.2000
Applicant's or agent's file reference: DM6919	IMPORTANT NOTIFICATION
International application No.: PCT/US99/00747	International filing date *(day/month/year)*: 14/01/1999
	Priority date *(day/month/year)*: 14/01/1998
Applicant: DU PONT PHARMACEUTICALS COMPANY	

FILE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer: Oberhauser, A
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tel.+49 89 2399-8139

CLS NOTED 5-22-2000 MISP

Form PCT/IPEA/416 (July 1992) NF1 7/14/2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DM6919		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/00747	14/01/1999	14/01/1998
International Patent Classification (IPC) or national classification and IPC		
A61K49/00		
Applicant		
DU PONT PHARMACEUTICALS COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/07/1999	10.05.2000
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Staber, B Telephone No. +49 89 2399 8587

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/00747

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-24 as originally filed

Claims, No.:

1-44 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 3, 5, 6, 10-14, 16, 18, 20-22, 26-35, 38, 39, 41-44
	No:	Claims	1, 4, 7-9, 15, 17, 19, 23-25, 36, 37, 40
Inventive step (IS)	Yes:	Claims	29-35
	No:	Claims	1-28, 36-44,
Industrial applicability (IA)	Yes:	Claims	1-44
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The documents are referred to in this written opinion are numbered as follows:

D1: EP-A-0 349 429 (CENTRE NAT RECH SCIENT) 3 January 1990 (1990-01-03)
D2: WO 95 32006 A (IMARX PHARMACEUTICAL CORP) 30 November 1995 (1995-11-30)
D3: WO 96 31196 A (IMARX PHARMACEUTICAL CORP) 10 October 1996 (1996-10-10)
D4: G. GREGODIADIS (EDITOR): 'Liposome Technology, Volume 1: Preparation of liposomes' 1984 , CRC PRESS, INC. , BOCA RATON, US XP002101586 13391 & D.W. DEAMER: 'PREPARATION OF SOLVENT VAPORIZATION LIPOSOMES'
D5: OHKI K ET AL: 'SHORT AND LONG RANGE CALCIUM-INDUCED LATERAL PHASE SEPARATIONS IN TERNARY MIXTURES OF PHOSPHATIDIC ACID PHOSPHATIDYLCHOLINE AND PHOSPHATIDYLETHANOLAMINE' HEMISTRY AND PHYSICS OF LIPIDS, 1989, VOL. 50, NO. 2, PAGE(S) 109-118., XP002101581
D6: WO 96 08234 A (IMARX PHARMACEUTICAL CORP) 21 March 1996 (1996-03-21)
D7: WO 96 40285 A (IMARX PHARMACEUTICAL CORP ;UNGER EVAN C (US); SHEN DEKANG (US); WU) 19 December 1996 (1996-12-19)
D8: WO 97 40858 A (IMARX PHARMACEUTICAL CORP) 6 November 1997 (1997-11-06)

Concerning the First Invention

The first invention of the present application is directed to a process for preparing a phospholipid suspension as set out in the claims 1 to 22 and to the resulting phospholipid suspension as defined in the product claims 36 to 44.

Novelty

Document D1 (EP-A-0 349 429) is concerned with a process for preparing a colloidal lipid suspension comprising the preparation of a lipid solution in a solvent, such as alcohol (e.g. ethanol) which is subsequently poured into an aqueous phase, then heated to remove the solvent (cf, D1, column 1, l. 39 to 55), and then subjected to a

filtration operation (cf. D1, Ex. 1).
It is further said that the concentration of the lipide in the solvent is between 0.1 to 10wt%.
Said document is therefore novelty destroying for claims 1, 7, 8, 9, 17, and 19.

Document D2 (WO-A-9 532 006) refers to contrast agents in the form of microspheres prepared from a gas(precursor) and stabilizing agents which are selected from phospholipids. The phospholipids preferably used are DPPC, PEG-DPPE, and DPPA which were introduced into a carrier solution of normal saline, glycerol and propylene glycol (cf. D2, p. 48, Example 1).
Even if the process mentioned in D2 is different from that described in the present invention, the resulting phospholipid suspension as defined in claims 36, 37 and 40 are identical with the mixture disclosed in D2.

Hence, claims 36, 37, and 40 are not novel with respect to D2.

Document D3 (WO-A-9 631 196) refers to the preparation of micelle compositions comprising the suspension of the liquid compound in an organic solvent, evaporation of the solvent, resuspension in an aqueous medium followed by sonification and centrifugation (cf. D3, p. 20, l.13 to 18).
Said method takes away novelty of present claims 1, 9, and 17.

In addition, Example 1 of D3 anticipates the phospholipid suspension as mentioned in claims 36, 37 and 40 of the invention.

Document D4 (G. GREGODIADIS (EDITOR): 'Liposome Technology, Volume 1: Preparation of liposomes' 1984 , CRC PRESS, INC. , BOCA RATON, US XP002101586 13391 & D.W. DEAMER: 'PREPARATION OF SOLVENT VAPORIZATION LIPOSOMES') refers to the so-called "solvent vaporization method" used in the production of liposomes comprising the following principle step: injecting diethyl ether, petroleum ether, or pentane solutions of phospholipids (or mixtures thereof) into an aqueous phase warmed to 60°C (cf. D4, p. 30, last paragraph). It is further reported that the resulting suspension can be filtered (cf. D4, p. 31, last paragraph).

D4 therefore takes away novelty of claims 1, 9, 15, 17, and 19.

Document D5 (OHKI K ET AL: 'SHORT AND LONG RANGE CALCIUM-INDUCED LATERAL PHASE SEPARATIONS IN TERNARY MIXTURES OF PHOSPHATIDIC ACID PHOSPHATIDYLCHOLINE AND PHOSPHATIDYLETHANOLAMINE' CHEMISTRY AND PHYSICS OF LIPIDS, 1989, VOL. 50, NO. 2, PAGE(S) 109-118., XP002101581) ic concerned with the preparation of a dispersion of a ternary phospholipid blend of DPPA, DPPC, DPPE comprising the preparation of a chloroform solution, evaporation of the solvent, followed by the introduction of the blend into an aqueous mixture of buffer and $CaCl_2$.
Said document is considered to be novelty destroying for claims 1, 4, and 9.

Document D6 (WO-A-9 608 234) is related to a container comprising an aqueous lipid suspension phase and separately a gaseous phase which after milting the two phases gas-filled liposomes will be formed. The lipid suspension of D1 contains DPPC, DPPA, and PEG-DPPE which is added to a diluent containing saline: propylene glycol : glycerol (8:1:1, v:v:v) (cf. D6, p.51, Example 1). Said lipid suspension takes away novelty of claims 36, 37 and 40 of the invention.

Example 6 of D7 (WO-A-9 640 285) comprises a phospholipid suspension prepared via a simple mixing operation and Example 1 of D8 (WO-A-9 740 858) which describes a lyophilized lipid composition, both documents anticipate the subject-matter of claimed product-by-process as set out in claims 36, 37, and 40.

Consequently, the subject-matter of claims 1,4, 7, 8, 9, 15, 17, 19 and 36, 37, and 40 do not fulfil the requirement of Article 33(2) EPC.

Inventive Step

The subject-matter of claims 2, 3, 5, 6, 10-14, 16, 18, 20-22, 38, 39, and 41 to 44 which is not explicitly disclosed in the above-mentioned documents, represents features which are advantageous when carrying out the claimed method. However, as fas as the Applicant failed to demonstrate that these features provoke unexpected effects or results, they are considered to come within the scope of the customary practice followed by a skilled person.

Hence, the subject-matter of claims 1 to 22 and claims 36 to 44 do not meet the requirement of Art. 33(3) PCT.

Clarity

Claim 1 does not fulfil the requirements of Art. 6 PCT since the term "the lipid blend **substantially** dissolves.." is not quite clear. Said unclear expression encompasses a solution wherein a lipid blend is completely dissolved up to 100% as required in the present specification (cf. p.13, l. 28 and p. 14, l. 16 and 37) as well as a lipid blend dissolved in the solvent in an amount of little more than 50% resulting in an inhomogeneous system.

Concerning the Second Invention

The second invention of the present application is concerned with a process for preparing a phospholipid suspension including step (1) to (7) as defined in claims 1 to 28.

Novelty

The mentioned-above, a process for preparing a phospholipid suspension comprising the steps (1), (2), (3) and (4) are already described in the prior art documents D1, D3, and D4.
Document D3 further describes that an inert gas in the form of perfluorocarbon, such as perfluoropropane is incorporated in the lipid compositions (cf. D3, p. 23, l.17/18; l. 29) by placing the composition in a vial of 1.1 ml headspace (cf. D3, Example 1).

In the light of D3, the subject-matter of claim 1, 9, 17, 23, 24 and 25 cannot considered to be novel.

Inventive Step

Document D3 does neither disclose the fact that exchange of headspace gas is

performed using a lyophilizing chamber, nor does it disclose that the vial is sterilized.

These measurements however are considered to be obvious modification of the process mentioned in D3 which cannot impart an inventive step to the process of claims 1 to 28.

Hence, claims 1 to 28 do not meet the requirements of Article 33(3) PCT.

Concerning the Third Invention

The third invention involved in the present application is the preparation of a lipid blend as defined in claims 29 to 35 using a so-called dissolution-precipitation procedure.

Novelty and Inventive Step

Since the available prior art documents do neither describe nor suggest the preparation of a lipid blend comprising an organic solvent dissolution-precipitation process, the claims 29 to 35 are considered to be novel and inventive.

Consequently, claims 29 to 35 fulfil the requirements of Art. 33(2) and 33(3) PCT.